PROBLEMS OF PHARMACEUTICAL PRODUCTION IN NIGERIA

L. USE OF CASSAVA STARCH IN PREPARATION OF ACETYLSALICYLIC ACID 300mg TABLETS

By

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ABSTRACT

Cassava starch has not yet achieved a wide spread pharmacopoeal acceptance compared to maize, rice and wheat starches, hence its application in the pharmaceutical industry is still so limited. In West Africa, particularly in Nigeria Cassava is in mass production as well as a popular food stuff for the natives. It was thought advisable to extract starch from Cassava flour and to use it in the preparation of Acelylsalicylic Acid* Tablets, testing its disintegration capacity, as well as its effects on the other physical properties of the tablets. Maize starch was used for comparison. Effect of using different concentrations of Cassava starch as a disintegrant on the physical parameters of Aspirin Tablets was also considered. Effect of Aspirin Granules fineness on the efficacy of Cassava as compared to maize starch was evaluated. From the results so far obtained Cassava starch can be used as a disintegrant and lubricant in the production of Aspirin Tablets and emphasis should be laid on using pure starch, right percentage concentration and suitable compression force to ensure that the tablets produced pass all the necessary physical tests.

INTRODUCTION

Cassava is a two species plant of spurge family (Euphorbiaceae), namely: the bitter Cassava (Manihot Esculenta) and sweet Cassava (Manihot Dulcis). Both have a large fleshy Cylinderical tapering root. The root is filled with milky juice and in the case of bitter Cassava root the juice contains cyanogenitic glycoside which is highly poisonous. In the preparation of Cassava flour the poison is rendered harmless by pressing out the juice and exposing the Cassava pulp to the sun heat which renders the poison harmless by converting it to prussic acid which escapes.

Starches are used for their swelling property as disintegrants in tablet manufacture, a property which we wanted to evaluate when using Cassava starch which was tested and found to comply with the European Pharmacopoeia requirements.

Borzunov et al., 1967 found that by increasing the contents of potato starch in tablets of bromisoval and terpine hydrate, firmness of tablets was diminished, their porosity increased, and their disintegration time was shortened. The disintegration of tablets was explained by improvement of their microcapillary system by the addition of starch.

H. Nogami et al, 1967 in a comprehensive study on the disintegration of Aspirin Tablets containing starch as disintegrating agent found among others that (1) The rate determining step of the disintegration was the water penetration into the tablet porous structure (2) Starch was able to develop the capillary structure in Aspirin Tablets (3) A critical amount of starch appeared necessary for the disintegration, which depended on the particle size of the SP. surface area of ingredients, the smaller the Aspirin particle size was, the larger was the starch amount required for disintegrating the tablets (the Aspirin Tablets of 11.9 u in mean particle size did not disintegrate by adding 20% starch) (4) When tablets disintegrated very rapidly and completely, their capillary wall was considered as starch (5) The model proposed for disintegration explained why the tablets made from the medium Aspirin particles (294 u in mean vol-surface particle diameter) disintegrated more rapidly than those containing the largest Aspirin particles (953 u)

K. C. Commons et al, 1968 performed disintegration tests on tablets compressed from 16/20, 40/60, and 60/80 mesh granulations prepared by the method of dry granulation to contain 250mg. of tolbutamide and corn starch concentrations of 6, 7, 8, 9 and 10% in each granulation size. It might be expected that disintegration time would decrease as the percent of starch in the tablet increased. This does not appear to be the case for tolbutamide tablets. Instead there appears to be a critical starch concentration for different granulation sizes.

It is to be noted that it is only the Brazilian and Portugese pharmacopoeas which included Cassava Starch in addition to the European Pharmacopoea Varieties. The Pharmaceutical Industry may be using those starches in preference to the Cassava starch, due to inavailability of Cassava in temperate regions. As it is not the case in West Africa, particularly in Nigeria, it was thought to extract starch from this cheap, easily obtainable and bulk produced comodity and to investigate its efficacy in the preparation of Aspirin Tablets.

Aspirin was selected for the study because it is a commonly used drug and secondly because it is commercially available in granule form, hence it can be directly compressed after mixing with starch into tablets. This will enable us to find the effect of Cassava starch on the tablet parameters, without interference of other excipients. The results were compared to those of Maize starch.

The use of Maize starch as the model disintegrant is due to works done by Hecht and Huyck (1964) and similar works done by Bergman and Bandelin (1964) which led to a conclusion that Maize starch was superior to other materials they used as disintegrants in their study.

MATERIALS AND METHODS

1. Preparation and Testing of Cassava Starch

Cassava flour is screened and suspended in water. The supernatant fluid containing the suspended particles is siphoned and allowed to settle for hours. The clear supernatant fluid is discarded and the residue is dried at room temperature. The dried mass was pulverised and sieved through a fine sieve This fine Cassava starch powder which complied to both B.P. 73 and Europ. Pharmacopoea was used in the different formulations done.

2. General Formula Per Each Tablet Batch

Active ingridient ......Aspirin granules (Graesser salic. Ltd.) 100gm., Disintegrant........Cassava or Maize starch...........2-10%w/w.

* Commonly known as Aspirin

3. Method of Preparation of Aspirin Tablets

Aspirin available for this study was in granule form, hence no problem concerning flow properties, as well as no need for a lubricant specially when we are using a fine material as a disintegrant.

For each batch of Aspirin tablets 100gm. of acetylsalicylic acid granules were mixed by the doubling up method with the appropriate amount of starch previously dried at 37°. The resulting mixture was finally mixed in a Roto mixer for 5 minutes and then compressed on a Diaf single punch machine using 9.5mm set of punches and dies. The filling volume was adjusted to accomodate the planned tablet weight and the hydraulic pressure was set to 9.5. A sample of 60 tablets was compressed every minute at a different compression force i.e. 4, $3\frac{2}{3}$, $3\frac{1}{3}$ 3 and at times $4\frac{1}{3}$. Every precaution was taken to compress the prepared granule mixture under the same conditions.

4. Quality Control Tests Run on The Prepared Tablets

(a) **Disintegration Test**
It was conducted using a Manesty disintegration apparatus which satisfies the B.P. 73 requirements. The disintegration time represented the average of two results.

(b) **Tablet Hardness**
A Monsanto hardness tester was used and the result represented the average of five readings. For good reproducibility the load on the tablet was increased at a standard rate and the method used by Shotton and Ganderton which satisfies this criterion was adopted.

(c) **Friability**
It was conducted on 10 tablets using Erweka friabilator. The tablets were tumbled for 4 minutes (100 revolutions), deducted then reweighed. The results were expressed as percentage weight/weight loss.

RESULTS AND DISCUSSION

1. Comparative Study of Cassava and Maize Starch as Disintegrants

This excercise was carried out by incorporating each starch separately with Aspirin Granules in 7, 8, 9 and 10 % w/w concentration. The mixture was compressed and tested for disintegration, hardness and friability (Table I).

The results indicate that at lower concentrations (7 & 8%), maize starch gave a lower disintegration time than cassava starch. The difference in the disintegration time between the two starches decreased rapidly as the concentration of the two starches increased to 9 & 10% where the values are nearly similar (Fig. I).

The disintegration time using both starches was affected by the tablet hardness, the harder the tablets the longer time it takes to disintegrate (Table I).

Seitz and Flessland, 1965 found that disintegration time of a tablet is a function of many factors among which are size, shape, weight, hardness, aging, size of granules and moisture content and since all these factors except hardness were hold constant throughout the experiment, and even since Aspirin Granules and starch were from the same containers and the tabletting machine set-up was similar, it is obvious that the difference in disintegration time is due to the type of starch used.

Hersey, J. A. reported that tablet hardness is affected by particle size, lubricant, adhesives, moisture content and entraped air. The investigation at this phase was a comparative one, finding the effect of different starches on tablet hardness using different pressures and keeping all factors mentioned by the above authors under the same conditions. The summarized results on Fig. II indicated that compared to maize starch, cassava starch produced harder aspirin tablets at all concentrations and compression forces. This might be due to stronger adhesive and cohesive properties of cassava starch. However it was noted that the difference in tablet hardness between the two starches become insignificant as the compression force neared 4, a criteria released by Shotto and Hersely who mentioned that the bonding of particles in tabletting are still not well understood due to a number of mechanisms. The characteristic of cassava starch at all concentrations is that a reasonable hardness is achieved at low compression pressures. This is vital where tabletting machines are supposed to operate at low pressure for maximum efficiency and long duration.

Results of friability (Table I) indicated that at all concentrations, Cassava starch in aspirin tablets gave better friability results, particularly at a compression force of $3\frac{1}{3}$. However there is no apparent relationship between crushing strength and friability values (Fig. III & IV). The same kind of result was obtained with the work done by Seitz and Flessland (1965).

Tablet capping was apparent at higher concentrations of both starches when applying high compression forces. Gunsel-et-al found that the effect of starch on capping is complex since many factors attribute to it, viz:- entrapped air, punches and dies, tabletting speed etc. The last two factors were constant during compression. So the capping might be explained by the fact that increasing the starch concentration affects the aspirin particle - particle bond.

Tablet appearance by the naked eye is similar whether using cassava or maize starch, however against a black background cassava starch gave glossiness to the tablets, particularly those compressed under high compression forces.

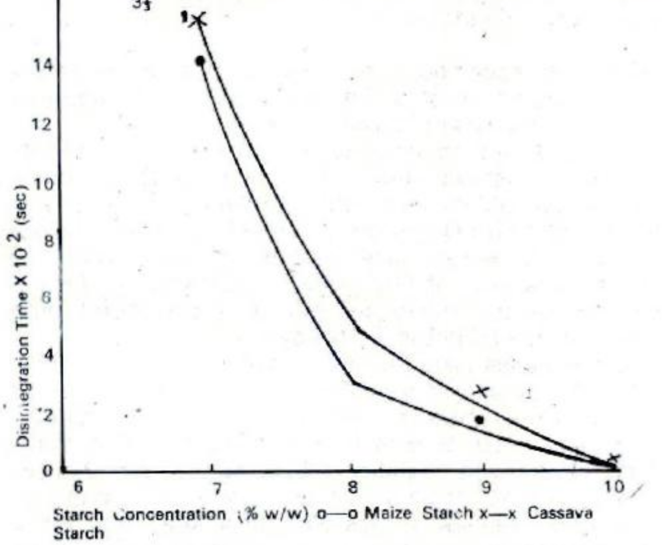
(ii) The Effect of Using Different Concentrations of Cassava Starch on the Physical Parameters of Aspirin Tablets

Considering the higher concentrations of cassava starch used in the first phase of that work, it was appropriate to see to the effect of lower concentrations 2, 4 and 6 per cent. The results are shown in table II.

The disintegration time of aspirin tablets containing starch decreases exponentially with increase in concentration (Fig. I). The tablets which contained concentrations of cassava starch below 7 per cent remained intact after 30 minutes in the disintegration tubes and this is particularly true for 2 and 4 per cent concentrations. With 6 per cent, tablet disrupted into large particles in less that 2 minutes, however these particles failed to pass through the mesh even after 30 minutes. Initial disruption of tablets was a characteristic common to all concentrations of cassava starch used, which indicated that the mechanism of action as a disintegrant was by swelling as earlier indicated by Petel and Hopple, 1960 for other starches they studied.

The most interesting feature of low concentrations (2 - 6 per cent) of cassava starch was that the hardness

Fig. i Effect of concentration of either Cassava or Maize Starch on the disintegration time of aspirin tablets, using a compression force of 3⅓



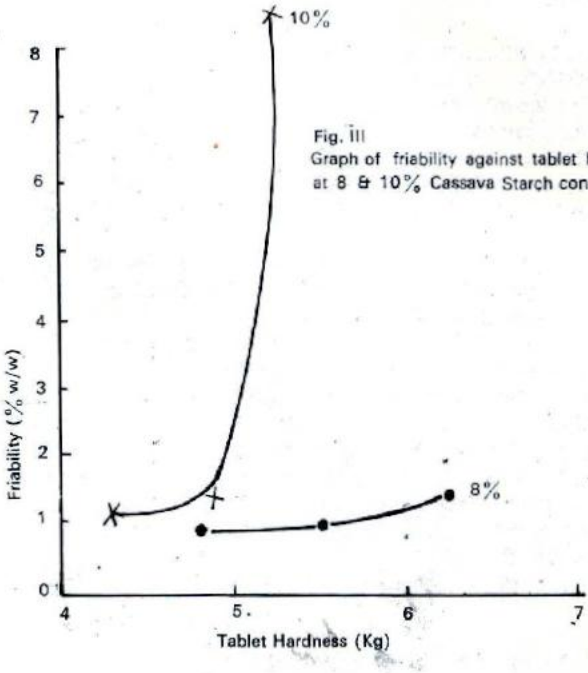
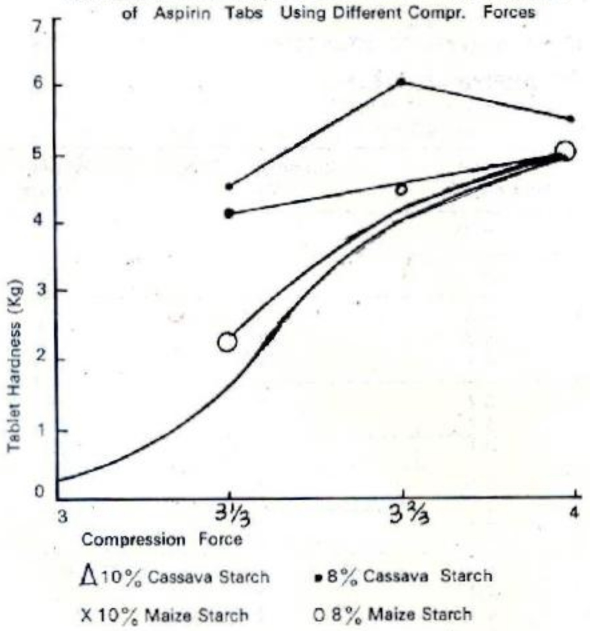


Fig. III
Graph of friability against tablet hardness at 8 & 10% Cassava Starch concentrations

Fig. ii Effect of Percentage of added Starch on the Hardness of Aspirin Tabs Using Different Compr. Forces



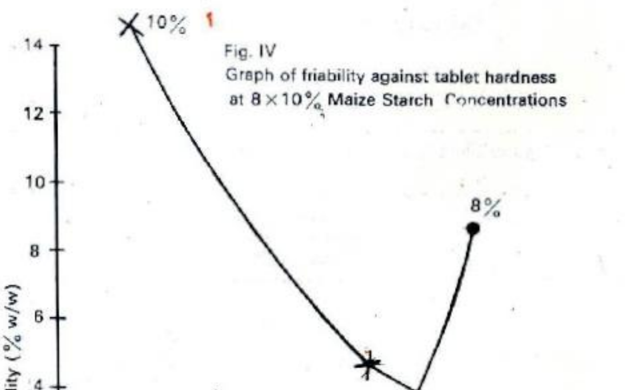


Fig. IV
Graph of friability against tablet hardness at 8 × 10% Maize Starch Concentrations

of aspirin tablets reached a maximum value at compression force $3\frac{2}{3}$, then declined as the force increased above that value.

Friability as noted is not a function of cassava starch concentration. High compression forces sometimes resulted in tablet capping and the tendency increased as the starch concentration increased. Except at 4 per cent concentration, there is a direct relationship between hardness and friability, a characteristic of cassava starch. Tablet appearance was good for all concentrations used.

(iii) The Effect of Particle Size of Aspirin Granules on the Physical Parameters of the Tablets Using either Cassava or Maize Starch.

This experiment was promoted by some preliminary trials, when it was found that increase in starch concentrations favoured quicker disintegration of tablets, but friability was high with rampant capping of some tablets. One factor which may have contributed to this is unsuitability of granule size distribution. This factor was investigated in the third part of this paper, with an attempt to evaluate the influence of 'fine' and 'normal' aspirin granules on the physical parameters of aspirin tablets when using either cassava or maize starch as disintegrants.

The 'normal' aspirin granules is the product supplied by Graesser salicylates Ltd. consisting of different particle sizes while the 'fine' granules is the portion that passes through the fine sieve of Diaf granulator where the particles are small and fairly even.

10 per cent starch was incoporated with the required amount of aspirin granules and then compressed under the same conditions. The tablets were tested and results twere compiled in table III.

Generally speaking, there is a slight decrease in the disintegration time of tablets when using fine granules, specially in the case of cassava starch.

As regards tablet hardness, the results (Fig. V) indicate that using cassava starch with fine aspirin granules gave harder tablets than with normal granules, but in the case of maize starch the difference is not so marked (Fig. VI). The reason may be that on compression the large surface area of fine granules helps the molecular and electrostatic forces to form a strong bond with cassava starch (Shotton & Hersey).

Both starches gave lower friability values with normal than with fine aspirin granules. Higher chances of tablet capping were observed with fine granules whatever starch was used. It was however found that cassava starch gave lower friability values and lesser chances of capping than maize starch on using either normal or fine asprin granules. It was also discovered that while friability increases with increase in compression force in case of cassava, it is the reverse in case of maize starch (table III).

TABLE 1

COMPARATIVE STUDY OF THE EFFECT OF USING CASSAVA AND MAIZE STARCHES AS DISINTEGRANTS ON THE PHYSICAL PARAMETERS OF ASPIRIN TABLETS

Percentage of Starch	*Type of Starch*	*Daif Machine Compression Force*	*Tablet Hardness (Kg)*	*Disintegration Time (Sec.)*	*Friability (% w/w)*
7	Cassava	$3\frac{1}{3}$	4.35	1590	0.9
	Maize	$3\frac{1}{3}$	3	1440	1.3
8	Cassava	4 $3\frac{2}{3}$ $3\frac{1}{3}$	5.5 6.2 4.7	540 853 509	1.0 1.5 1.0
	Maize	4 $3\frac{2}{3}$ 33	5.2 4.2 2.4	165 154 314	8.3 1.2 1.2
9	Cassava	$3\frac{1}{3}$	4.05	244	1.0
	Maize	$3\frac{1}{3}$	2.8	160	1.3
10	Cassava	4 $3\frac{2}{3}$ $3\frac{1}{3}$	5.2 4.8 4.3	17 18 16	8.3 1.2 1.1
	Maize	4 $3\frac{2}{3}$ $3\frac{1}{3}$ 3	5.2 4.1 1.7 0.35	25 11 8.0 —	2.8 4.7 14·2 —

TABLE II

EFFECT OF USING DIFFERENT CONCENTRATIONS OF CASSAVA STARCH AS A DISINTEGRANT ON THE PHYSICAL PARAMETERS OF ASPIRIN TABLETS

Percentage of Cassava Starch	*Diaf Machine Compression Force*	*Tablet Hardness (Kg)*	*Disintegration Time (Seconds)*	*Friability (% w/w)*
2	4	5.2	> 1800	0.9
	$3\frac{2}{3}$	6.8	" "	1.0
	$3\frac{1}{3}$	3.1	" "	1.0
4	4	5.5	" "	3.2
	$3\frac{2}{3}$	6.7	" "	0.8
	$3\frac{1}{3}$	4.75	" "	2.2
6	4	5.1	" "	1.3
	$3\frac{2}{3}$	6.75	" "	2.0
	$3\frac{1}{3}$	5	" "	1.1
7	$3\frac{1}{3}$	4.35	1590	0.9
8	4	5.5	540	1.0
	$3\frac{2}{3}$	6.2	853	1.5
	$3\frac{1}{3}$	4.7	509	1.0
9	$3\frac{1}{3}$	4.05	244	1.0
10	4	5.2	17	8.3
	$3\frac{2}{3}$	4.8	18	1.2
	$3\frac{1}{3}$	4.3	16	1.1

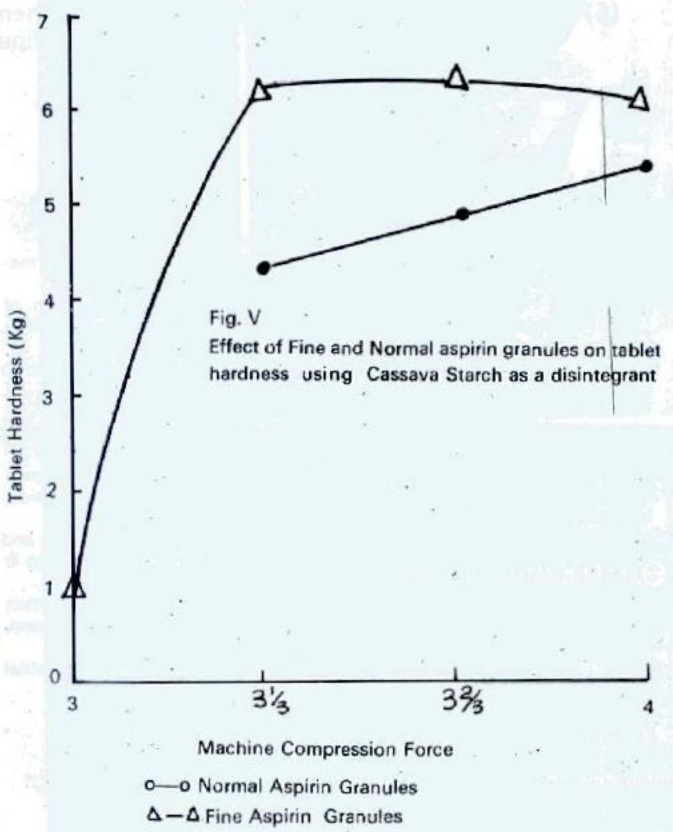


Fig. V
Effect of Fine and Normal aspirin granules on tablet hardness using Cassava Starch as a disintegrant

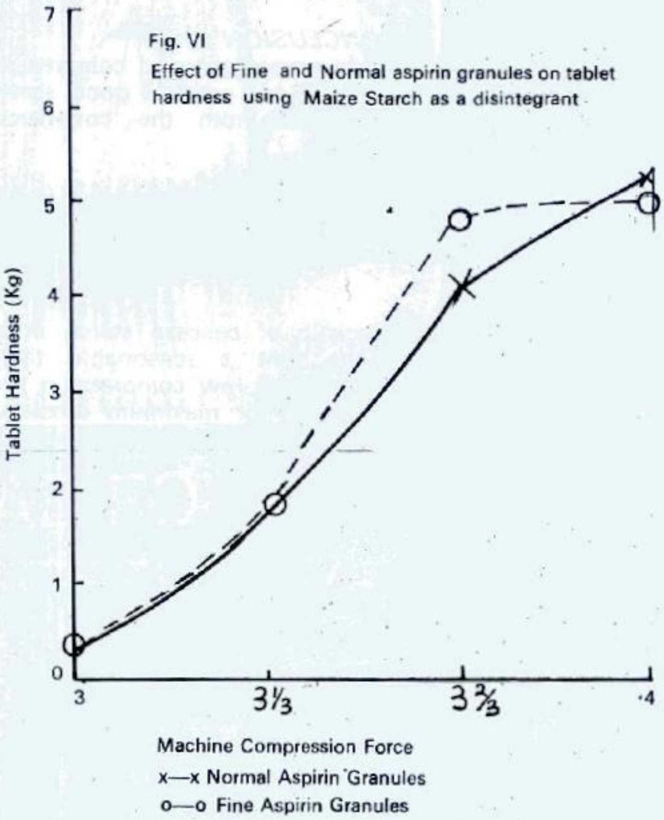


Fig. VI
Effect of Fine and Normal aspirin granules on tablet hardness using Maize Starch as a disintegrant

TABLE III

EFFECT OF USING 'FINE' & 'NORMAL' ASPIRIN GRANULES ON THE PHYSICAL PARAMETERS OF ASPIRIN TABLETS USING 10% OF EITHER CASSAVA OR MAIZE STARCH AS A DISINTEGRANT

Aspirin Granule Type	*Type of Starch*	*Dial Machine Compression Force*	*Tablet Hardness (Kg)*	*Disintegration Time (Sec.)*	*Friability (% w/w)*	*Remarks*
'Normal'	Cassava	4	5.2	17	8.3	—
		$3\frac{2}{3}$	4.8	18	1.2	
		$3\frac{1}{3}$	4.3	16	1.1	
	Maize	4	5.2	25	2.8	Capping occurred both in production and friabilator.
		$3\frac{2}{3}$	4.1	11	4.7	
		$3\frac{1}{3}$	1.7	8	14.2	
		3	0.35	—	All broken	
'Fine'	Cassava	4	5.9	12	18.1	Some tablets capped at high compression forces.
		$3\frac{2}{3}$	6.3	16	3.7	
		$3\frac{1}{3}$	6.2	10	1.1	
		3	1	12	All broken	
	Maize	4	5	18	4.4	Capping of tablets were rampant at both low and high compression forces.
		$3\frac{2}{3}$	4.8	13	5.1	
		$3\frac{1}{3}$	1.7	9	1.8	
		3	0.4	—	—	

Therefore, whenever using 10 per cent of starch as a disintegrant with aspirin granules, cassava starch is preferable to get a suitable tablet hardness, low friability and less tendency to capping.

CONCLUSION

(1) Using the right percentage and compression force, cassava starch can produce good acetylsalicylic acid tablets from the commercial granules.

(2) Compared to maize starch, cassava starch produced harder aspirin tablets at all concentrations and compression forces.

(3) The characteristic of cassava starch at all concentrations is that a reasonable tablet hardness is achieved at low compression pressures which is vital for maximum efficiency and long duration of tabletting machines.

(4) Generally speaking cassava starch gave glossy and less friable aspirin tablets.

(5) Decreasing the percentage of cassava starch in the aspirin formulation led to an exponential increase in the disintegration time. As from 7 per cent downwards the tablets failed the test. Concerning hardness it reached a maximum value at compression force $3\frac{2}{3}$, then declined as the force increased above that value. Friability as noted is not a function of cassava starch concentration.

(6) Normal aspiring granules are better when used for production of the tablets than the fine ones.

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